# SYNTHESIS OF SULFOCHLORIDE DERIVATIVES OF THE ARYL OXYALKYL CARBOXYLIC ACIDS AS INTERMEDIATES IN OBTAINING COMPOUNDS WITH BIOLOGICAL POTENTIAL

## SINTEZA SULFOCLORURILOR ACIZILOR ARIL-OXIALCHIL CARBOXILICI CA INTERMEDIARI ÎN OBȚINEREA UNOR COMPUȘI CU POTENȚIAL BIOLOGIC

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***Abstract***. *Aryl - oxyalkyl carboxylic acids and their derivatives are compounds with high biologic potential, having various pharmacological properties or auxin - type growth regulator action. The pharmacological tests determined that the presence of substituted or unsubstituted sulphonamidic groups in the phenoxyacetic derivatives confers them a toxicity which in most cases is negligible; they also have high bioavailability and can be used as effective growth stimulants for various plant species at low concentrations. Since the $R_1$, $R_2$ - substituted phenoxyacetic acid esters and their sulfochlorides are intermediates used in the synthesis, this paper presents the general scheme of the process for the chlorosulfonation of the considered aryl - oxyalkyl carboxylic esters, the mechanism of the reaction, the obtaining method and the sulfochlorides yields for the methyl esters of fenil-1,2-dioxiacetic, fenil-1,3-dioxiacetic și fenil-1,4-dioxiacetic acids in the reaction with the chlorosulfonic acid.*

***Key words***: *phenoxyacetic, methyl esters, sulphochloride, growth regulator*

***Rezumat***. *Acizii aril-oxialchil carboxilici și derivații lor fac parte dintre compușii chimici cu un potențial biologic ridicat, având diverse proprietăți farmacologice sau regulatoare de creștere de tip auxinic. Prin teste farmacologice efectuate asupra compușilor sintetizați s-a determinat că prezența grupărilor sulfonamidice, substituite sau nesubstituite, în moleculele derivaților fenoxiacetici conferă produselor finale o toxicitate de cele mai multe ori neglijabilă; de asemenea, au o biodisponibilitate ridicată și pot fi folosite ca produse stimulatoare de creștere eficiente pentru diverse specii de plante, în concentrații mici. Deoarece atât esterii acizilor fenoxiacetici $R_1$,$R_2$-substituiți cât și sulfoclorurile acestora sunt intermediari folosiți în sinteză, în această lucrare au fost realizate studii referitoare la schema generală a procesului de clorosulfonare pentru esterii aril-oxialchil carboxilici luați în considerare, mecanismul de reacție, metoda de obținere și randamentele în sulfocloruri pentru esterilor metilici ai acizilor fenil-1,2-dioxiacetic, fenil-1,3-dioxiacetic și fenil-1,4-dioxiacetic în reacția cu acidul clorsulfonic.*

***Cuvinte cheie***: *fenoxiacetic, esteri metilici, sulfoclorură, regulator creștere*

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The aryl - oxyalkyl carboxylic acids and their derivatives are chemical compounds with high biologic potential, having various pharmacological properties. Numerous compounds from this class enter into the composition of drugs with different use:

- the radical of the 2,3-dichloro phenoxyacetic acid is contained in the structures of two diuretic drugs: *Tricrinafen* and *Edecrin*;

- the radical of the 2,6-dichloro phenoxyacetic acid enters in the structure of *Lofexidine*, with central antihypertensive action;

- various anti-inflammatory drugs have phenoxyacetic or α-phenoxypropionic structure: *Ibufenac* (derives from phenoxyacetic acid), *Paduden* (derives from α-phenoxypropionic acid), *Aclofenac*, *Fenclofenac*, *Fenprofen*, *Percluson*;

- A number of products with antibacterial activity have in their structure phenoxyacetic radicals (*Penicillin V*), α-phenoxypropionyl (*Feneticiline*) and α-phenoxybutyryl (*Propiciline*);

- *Meclofenoxat* with a psycho energizing action is a derivative of p-chloro phenoxyacetic acid, as well as Iproclozide, used as an analeptic for the thymus (Oniscu, 1988);

- a number of derivatives of phenoxyisobutyric acid have lipid-lowering properties: *Beclobrat*, *Clofibrat*, *Fenofibrat*, *Teofibrat*;

Some phenoxyalkyl carboxylic derivatives have remarkable applications in agriculture, like the acids: 2,4- dichloro phenoxyacetic (2,4-D acid), 2,4,5-trichloro phenoxyacetic (2,4,5-T acid) with selective herbicide action and α-(2,4,5-trichloro phenoxy)-propionic acid (2,4,5-TP acid) used as selective herbicide in corn and cotton cultures.

Used in small doses, these products have growth regulating action. In case of exceeding the effective dose, phenoxyacetic acids turn into defoliants. For example, the 1 : 1 mixture between 2,4,5-T acid and 2,4-D acid butyl esters was used by U.S.A. as defoliant in the Vietnam War, under the name of “orange agent” (Neamtu and Irimie, 1991).

The α-(2-methyl, 4-chloro phenoxy)-propionic acid (2M-4CP acid) destroys weeds resistant to other herbicides, being used in cereal crops protection.

The α-(2,4-dichloro phenoxy)-propionic acid (2,4-DP acid) stimulates fruit growth and prevents their fall before harvest (Comanita et all., 1986).

A series of γ-phenoxybutyric acids are highly selective herbicides: γ-(2,4-dichloro phenoxy)-butyric acid (2,4-DB acid) or γ-(2-methyl, 4-chloro phenoxy)-butyric acid (MCPB acid) etc.

C. Oniscu and coworkers synthesized a series of esters, amides and hydrazides of the phenoxyalkyl carboxylic acids, as well as derivatives of the phenoxyalkyl carboxylic acids with sulphonamide group (Oniscu, 1968; Botez and Oniscu, 1972), which represent a new class of growth stimulators. From this class of compounds, two substances with auxinic action were tested in sugar beet, carrots, grapevine, and roses cultures, with remarkable results, allowing the product 2-sulphonamide, 4-chloro phenoxy-acetic acid's approval as sugar beet crop growth stimulator under the name of ASFAC.

Pharmacological tests performed on other novel compounds synthesized by the same group determined that their toxicity is almost zero; also they have a high bioavailability and remarkable neurostimulation, antidepressants and anticonvulsants properties (Nigovic et all., 1996).

A particularly valuable compound obtained from research in the class of phenoxyalkyl carboxylic sulphonamides derivatives is dimethylaminoethyl hydrochloride ester of the 2-chloro-4-sulphonyl dimethylamido phenoxyacetic acid (Romener), an efficient metabolic regulator of nerve cell, energizer, antidepressant and antipsychotic.

## MATERIAL AND METHOD

The general scheme for obtaining the derivatives of aryl- oxyalkyl carboxylic sulphonamides comprises the following steps:

- R-phenoxyacetic acids obtained from the corresponding phenols by condensation with monochloroacetic acid in an alkaline solution (NaOH);
- obtaining the methyl, ethyl etc. esters of these acids;
- esters' chlorosulfonation;
- chlorosulfonated esters' condensation with ammonia, substituted amines or other compounds with amino groups (Dumitrascu, 1998)

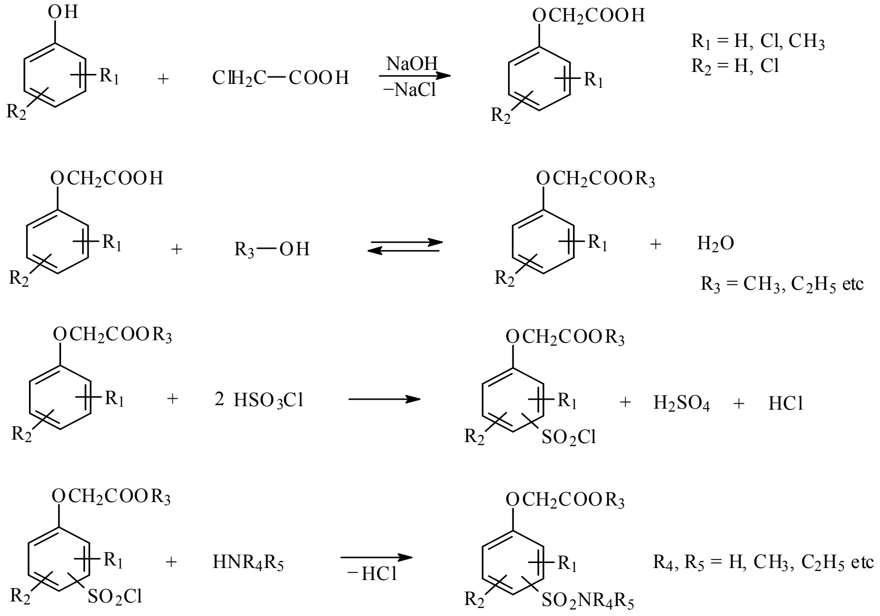

**Fig. 1** - The reaction scheme for obtaining sulphonyl amido-phenoxyacetic derivatives

The same steps of the general scheme for obtaining the derivatives of aryl oxyalkyl carboxylic acids sulphonamides are followed also to synthesize compounds containing in their structure two oxyacetic groups grafted in various positions of the aromatic nucleus.

Since the R1, R2-substituted phenoxyacetic acid esters and their sulfochlorides are intermediates used in the synthesis of all the compounds prepared by the sequence of reactions described above, studies were conducted on obtaining them.

Chlorosulfonation reaction mechanism, according to the literature (7), is shown in the diagram below (fig. 2) indicating that in the first step takes place the sulphonation with $SO_3$ and in the next step the sulphonic acid is converted to sulphochloride.

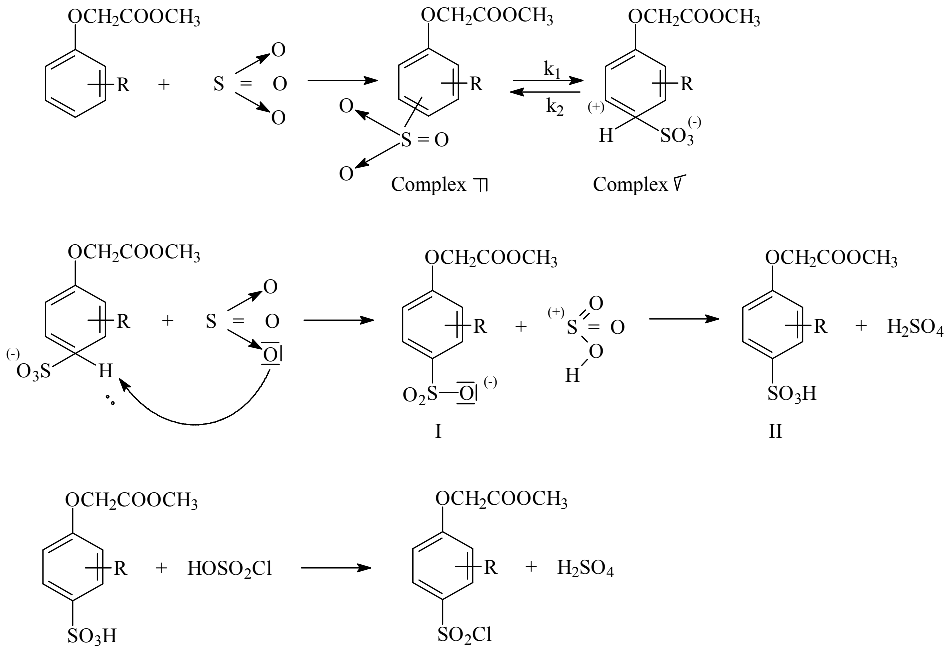

**Fig. 2** - Chlorosulfonation reaction mechanism

Obtaining the sulfochlorides of the phenoxyacetic and phenyl-dioxyacetic acids methyl esters was performed according to the scheme shown in figure 1.

The general procedure for preparation is as follows:

- over 0.7 moles of chlorosulfonic acid cooled to 0 - 50°C are added in small portions, with continuous stirring, 0.1 moles methyl ester, so that the temperature does not exceed 5$^0$C;

- after the addition of the ester, the reaction mixture is maintained at the same temperature 30 - 40 min and then the temperature is raised to values specific to the type of the ester, maintaining the temperature for 90 - 100 minutes, when the formation of the sulphochloride takes place;

- finally, the mixture is cooled to 5 - 6$^0$C and poured into a mixture of water and ice, under vigorous stirring, to destroy the unreacted chlorosulfonic acid and to precipitate the sulphochloride;

- the obtained sulfochloride is filtered, water washed until pH = 6.5, is recrystallized from a mixture of water - acetone (2: 1 volume ratio) or benzene, then is dried at temperatures $\leq 40^0$C.

# RESULTS AND DISCUSSIONS

According to the literature data on the chlorosulphonation of the aryl-oxyacetic acids (Oniscu, 1968), the chlorosulphonation of the phenyl dioxyacetic esters with chlorosulphonic acid is a process of pseudo equilibrium which can be kinetically described by the equation:

$$\frac{C_{SCl}}{C_{E_S}} = \frac{k_1}{k_2} \frac{C_{E_0}(M-1) - C_{SCl}}{C_{C_0} + C_{SCl}} \qquad (5)$$

in which: $C_{SCl}$=momentary concentration in sulphochloride (moles/l); $C_{Es}$ = momentary concentration in sulphonic ester (moles/l); $C_{Eo}$ = initial concentration of the ester (moles/l); $C_{Co}$=initial concentration of the sulfuric acid in the chlorosulphonic acid; M=the ratio between the concentration of the chlorosulphonic acid and the ester's concentration; $k_1$=rate constant for the formation of sulphochloride (l/moll·h); $k_2$=rate constant for the transformation of sulphochloride into sulphonic acid, determined by the sulfuric acid (l/mol · h).

Also, the literature (Oniscu, 1968) states that the molar ratio between the aryl-oxyalkyl carboxylic esters and the chlorosulfonic acid in the process of chlorosulphonation is 1:7. Based on these data, we initially set the optimal value in the chlorosulphonation process of the phenyl dioxyacetic esters of 1: 6. Under these circumstances, we observed the influence of reaction temperature on the chlorosulphonation of the phenyl dioxyacetic esters.

The chlorosulphonation of the ***phenyl-1,2-dioxyacetic acid's methyl ester*** was done by treating 0.6 mole of chlorosulphonic acid to 0.1 moles ester at a temperature of 0 - 5$^0$C. After merging the reactants, we raised the temperature at different values and then maintained it for one hour. Finally, the reaction mixture was diluted with ice + water mixture when the sulphochloride ester is separated.

We worked with temperature between 15 – 35$^0$C, and the obtained results are presented in table 1.

*Table1.*

| **Temperature ($^0$C)** | 15 | 20 | 25 | 30 | 35 |
|---|---|---|---|---|---|
| **η (%)** | 55 | 75 | 86 | 94 | 88 |

The chlorosulphonation of the ***phenyl-1,3-dioxyacetic acid's methyl ester*** followed the same steps described above, with the completion of the reaction at temperatures in the range of 10 – 25$^0$C. The obtained results are presented in table 2.

*Table 2.*

| **Temperature ($^0$C)** | 10 | 15 | 20 | 25 |
|---|---|---|---|---|
| **η (%)** | 60 | 85 | 92 | 89 |

The chlorosulphonation of the ***phenyl-1,4-dioxyacetic acid's methyl ester*** was also carried out under the conditions shown above and the completion of the reaction was carried out at temperatures between 35 – 60$^0$C, for one hour. The obtained results are presented in table 3.

*Table 3.*

| **Temperature ($^0$C)** | 35 | 40 | 45 | 50 | 60 |
|---|---|---|---|---|---|
| **η (%)** | 32 | 60 | 72 | 80 | 75 |

Representing graphically using the coordinates η - t$^0$C, the data presented in the tables above shows that for each case there is an optimum temperature range (fig. 3).

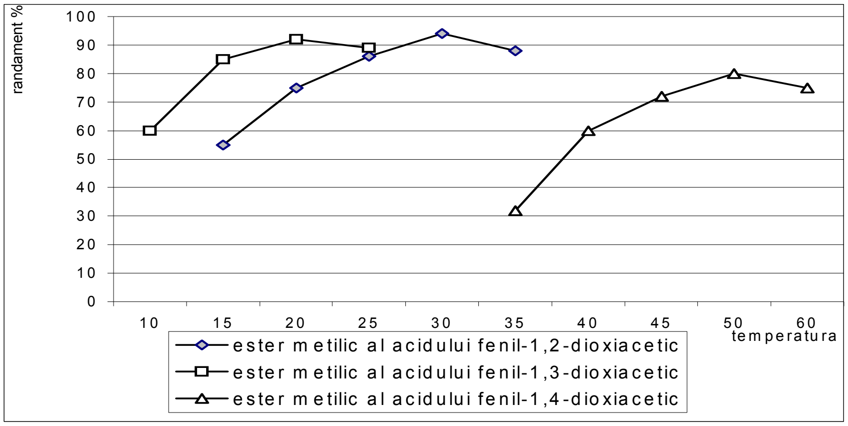

**Fig. 3** - The variation of efficiency with temperature in the chlorosulphonation process

The minimum reaction temperature, of approximately 20$^0$C, is noted for the phenyl-1,3-dioxyacetic ester, fact explained by the concurring orientation of the two oxyacetic acid groups existing in the phenyl ring.

## CONCLUSIONS

1. The molar ratio between the reactants in the chlorosulphonation process was established at 1:6 (dioxyacetic ester:chlorosulphonic acid);

2. The optimum reaction temperatures for the three obtained esters were: 30$^0$C for the phenyl-1,2-dioxyacetic acid's methyl ester when we obtained the best efficiency value – 94%, 20$^0$C for the phenyl-1,3-dioxyacetic acid's methyl ester when we obtained the highest efficiency value of 92% and 50$^0$C for the phenyl-1,4-dioxyacetic acid's methyl ester when we obtained 80% efficiency.

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